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**Prognostic Significance of Nonobstructive Left Main Coronary Artery  
Disease in Women Versus Men: Long-Term Outcomes From the CONFIRM  
(Coronary CT Angiography Evaluation For Clinical Outcomes: An  
International Multicenter) Registry**

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## Prognostic Significance of Nonobstructive Left Main Coronary Artery Disease in Women Versus Men

### Long-Term Outcomes From the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) Registry

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**Background**—Patients with obstructive ( $\geq 50\%$  stenosis) left main (LM) coronary artery disease (CAD) are at high risk for adverse events; prior studies have also documented worse outcomes among women than men with severe multivessel/LM CAD. However, the prognostic significance of nonobstructive ( $1\%–49\%$  stenosis) LM CAD, including sex-specific differences, has not been previously examined.

**Methods and Results**—In the long-term CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) registry, patients underwent elective coronary computed tomographic angiography for suspected CAD and were followed for 5 years. After excluding those with obstructive LM CAD, 5166 patients were categorized as having normal LM or nonobstructive LM (18% of cohort). Cumulative 5-year incidence of death, myocardial infarction, or revascularization was higher among patients with nonobstructive LM than normal LM in both women and men: women (34.3% versus 15.4%;  $P < 0.0001$ ); men (24.6% versus 18.2%;  $P < 0.0001$ ). A significant interaction existed between sex and LM status for the composite outcome ( $P = 0.001$ ). In multivariable Cox regression, the presence of nonobstructive LM plaque increased the risk for the composite outcome in women (adjusted hazard ratio, 1.48;  $P = 0.005$ ) but not in men (adjusted hazard ratio, 0.98,  $P = 0.806$ ). In subgroup analysis, women with nonobstructive LM CAD had a nearly 80% higher risk for events than men with nonobstructive LM CAD (adjusted hazard ratio, 1.78;  $P = 0.017$ ); sex-specific interactions were not observed across other patterns (eg, location or extent) of nonobstructive plaque.

**Conclusion**—Nonobstructive LM CAD was frequently detected on coronary computed tomographic angiography and strongly associated with adverse events among women. Recognizing the sex-specific prognostic significance of nonobstructive LM plaque may augment risk stratification efforts. (*Circ Cardiovasc Imaging*. 2017;10:e006246. DOI: 10.1161/CIRCIMAGING.117.006246.)

**Key Words:** coronary computed tomographic angiography ■ incidence ■ left main ■ nonobstructive coronary artery disease ■ sex disparities in coronary heart disease

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Obstructive left main (LM) coronary artery disease (CAD), defined as  $\geq 50\%$  luminal stenosis, is associated with significant morbidity and mortality.<sup>1</sup> Although the prevalence and burden of obstructive CAD is higher among men, prior studies have described worse outcomes among women than among men with severe multivessel or LM CAD, including after revascularization.<sup>2–5</sup> Despite abundant prognostic evidence regarding patients with obstructive LM CAD, clinical outcomes of patients with nonobstructive (1%–49% luminal stenosis) LM CAD, including sex-specific differences, have not been previously evaluated.

### See Editorial by Taqueti and Blankstein Clinical Perspective

Importantly, nonobstructive CAD is frequently identified on coronary angiography among patients with stable ischemic heart disease and is more prevalent in symptomatic women ( $\approx 60\%$ ) than in men ( $\approx 30\%$ ).<sup>4,6,7</sup> Furthermore, recent investigations have described a strong association between nonobstructive CAD and adverse cardiovascular events in both invasive and noninvasive angiographic cohorts; however, comparative prognostic data of women versus men with nonobstructive CAD are limited.<sup>8–14</sup> These findings have prompted increased efforts to examine the importance of nonobstructive CAD, including characterizing sex-related differences in outcomes, as a means to improve prognostic models and more precisely identify at-risk patients to target preventive care.<sup>7</sup> Notably, nonobstructive plaque within the LM has not been an emphasis within any of these studies to date.

Accordingly, we sought to determine the prognostic significance of nonobstructive LM CAD in a large, real-world cohort of patients who underwent elective coronary computed tomographic angiography (CCTA) for the evaluation of suspected CAD. Our objectives were to (1) assess the association between nonobstructive LM CAD and clinical outcomes, including all-cause mortality, nonfatal myocardial infarction (MI), and coronary revascularization; and (2) determine whether sex-specific differences in outcomes exist among patients with nonobstructive LM CAD and compared with other subgroups of nonobstructive CAD.

## Methods

### Study Cohort

In the long-term phase of the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) registry, a total of 12 086 stable outpatients underwent elective CCTA for evaluation of clinically suspected CAD and had prospective follow-up extended to 5 years. A total of 17 participating sites from 9 countries enrolled patients between 2002 and 2009. All sites received institutional review board approval and oversight, and all patients provided informed consent. Patient and site identifiers were not entered into the CONFIRM database. Additional details regarding the CONFIRM registry's design, rationale, site eligibility, and patient recruitment have been previously described.<sup>15</sup>

The inclusion criteria for our analysis reflected the enrollment indications of the CONFIRM registry, including (1) adults  $\geq 18$  years of age, (2) referral for CCTA to evaluate for suspected CAD given presenting symptoms or for risk stratification using a  $\geq 64$ -detector row scanner, (3) prospective data collection of CAD risk factors and CCTA data, and (4) standardized reporting of segmental coronary stenosis, as per Society of Cardiovascular Computer Tomography

guidelines.<sup>16,17</sup> Excluded from our study were patients with obstructive LM CAD or missing LM stenosis severity ( $n=1147$ ), history of known CAD, previous percutaneous coronary intervention, or previous coronary artery bypass surgery ( $n=1416$ ), and incomplete adjudication of clinical events ( $n=4357$ ) for a final cohort size of 5166 patients. All CONFIRM investigators have reviewed and approved our study.

### Clinical Descriptive Data

All patients enrolled in CONFIRM underwent evaluation by a physician or nurse prior to CCTA. Each participating site uniformly collected self-reported baseline clinical data, including age, sex, history of hypertension, diabetes mellitus, hyperlipidemia, smoking status, early family history of early CAD (father  $<55$  or mother  $<65$  years of age), left ventricular ejection fraction, and presenting symptom characteristics categorized as no chest pain, nonanginal chest pain, atypical angina, or typical angina.

### CCTA Protocol and Anatomic Definitions

Each CONFIRM site was directed by a level III-trained expert in CCTA and followed standardized protocols for performing CCTA as defined by guidelines of the Society of Cardiovascular Computer Tomography.<sup>16,17</sup> The percent luminal stenosis in the LM was coded as normal (0% stenosis) or nonobstructive (1%–49% stenosis) by visual assessment. Luminal stenosis in non-LM vessels, including the left anterior descending artery, left circumflex artery, and right coronary artery were also gathered and coded as normal, nonobstructive, or obstructive ( $\geq 50\%$  stenosis), which were consistent with previous CCTA-derived definitions for obstructive and nonobstructive CAD.<sup>2</sup> At all laboratories, intra- and inter-reader reliability were routinely assessed and have been previously described in detail.<sup>15</sup>

### Outcome Data Collection and Follow-Up Methods

Our primary outcome was a composite of incident all-cause mortality, nonfatal MI, or late coronary revascularization occurring  $>90$  days from the index CCTA. Each individual end point was also evaluated as a secondary outcome. The National Death Index was queried for all-cause death within the United States or determined through direct interview with the patient's family or physician, telephone call, or review of medical records for events outside of the United States. MI events were confirmed through review of the patient's medical records for hospital documentation of biomarker elevation and electrocardiographic alterations consistent with the Universal Definition of MI.<sup>18</sup> Coronary revascularization events were also confirmed through review of medical records; however, target vessel revascularization was not reported. Only late ( $>90$  days from the index CCTA) revascularization events were used as an end point; earlier revascularization events represent continued evaluation of the index but stable CAD course for a patient, whereas use of late revascularization is a common means to separate elective versus nonelective conditions and is consistent with prior literature.<sup>15</sup> Additional information on ascertainment and adjudication methods have been previously described.<sup>15</sup>

### Statistical Analysis

Using  $\chi^2$  tests for categorical variables and  $t$  tests for normally distributed or Wilcoxon tests for non-normally distributed continuous variables, baseline characteristics were compared between patients with normal LM and nonobstructive LM. We estimated time to event using the Kaplan–Meier method and compared differences in cumulative incidence of events between LM groups with log-rank tests.

Next, we tested for an interaction between sex and LM status for the study end points and examined sex-specific differences in outcomes according to LM status. After meeting the proportional hazards assumption by graphical assessment, 4 multivariable Cox proportional hazards models were created using covariables defined a priori based on clinical judgment. Model 1 included age, hypertension, diabetes mellitus, hyperlipidemia, smoking history, and the presence of typical angina to control for baseline demographics,

CAD risk factors, and pretest probability for obstructive CAD. Model 2 included the covariables from model 1 plus the number of non-LM coronary vessels with obstructive plaque to adjust for differences in obstructive plaque burden between LM strata. As an alternative method to adjust for co-occurring obstructive plaque, model 3 included the covariables from model 1 plus the total number of non-LM coronary artery segments with obstructive plaque. Finally, model 4 expanded on the previous models with inclusion of the segment involvement score (scored 0–15, excluding LM), which accounts for overall CAD burden by measuring both nonobstructive and obstructive plaque extent.<sup>19</sup>

We performed several subgroup and sensitivity analyses to test the robustness of our findings. (1) We assessed time to event by LM status in a subset of 3325 patients without any obstructive CAD to further account for baseline differences in plaque burden. (2) In the same subset, we examined whether sex-specific differences in risk varied based on the location (LM, left anterior descending artery, left circumflex artery, or right coronary artery) or extent (per-segment and per-vessel) of nonobstructive plaque. (3) To assess for potential selection bias, the baseline characteristics of patients who were excluded (n=6920) were compared with those included in the final cohort. We repeated survival analysis on the entire pooled cohort for the end point of all-cause mortality, which was the only outcome completely adjudicated in CONFIRM. (4) Because target vessel revascularization was not known and may have been subject to biases by sex or the extent of obstructive CAD, we removed revascularization from the composite end point and repeated the survival analysis using death or nonfatal MI as the primary outcome. A 2-tailed *P* value <0.05 was considered statistically significant for each analysis. All statistical analyses were performed using SAS version 9.4 (Cary, NC).

## Results

### Clinical and CCTA Characteristics of the Study Cohort

Of 5166 patients, 82% had normal LM and 18% had nonobstructive LM CAD (Table 1). Patients with nonobstructive LM were older and had higher baseline rates of CAD risk factors, including hypertension, diabetes mellitus, and hyperlipidemia (*P*<0.001). Furthermore, patients with nonobstructive LM CAD had more extensive co-occurring obstructive plaque and higher segment involvement score (*P*<0.001). Neither baseline left ventricular ejection fraction (*P*=0.232) nor presenting symptoms (*P*=0.424) were significantly different by LM status.

### Estimating the Risk of Death, MI, or Revascularization

Through a mean 5.3±1.8 years (median 5.5, interquartile range 5.1–6.2 years) of follow-up, there were 349 deaths, 471 nonfatal MIs, and 364 revascularization events. Cumulative 5-year incidence of the composite outcome was 27.3% for patients with nonobstructive LM CAD compared with 17.2% for patients with normal LM (*P*<0.0001; Figure 1). Differences in the incidence for the individual end points of all-cause mortality, nonfatal MI, and late coronary revascularization by LM status are also displayed.

**Table 1. Baseline Characteristics of Study Cohort by Left Main Status**

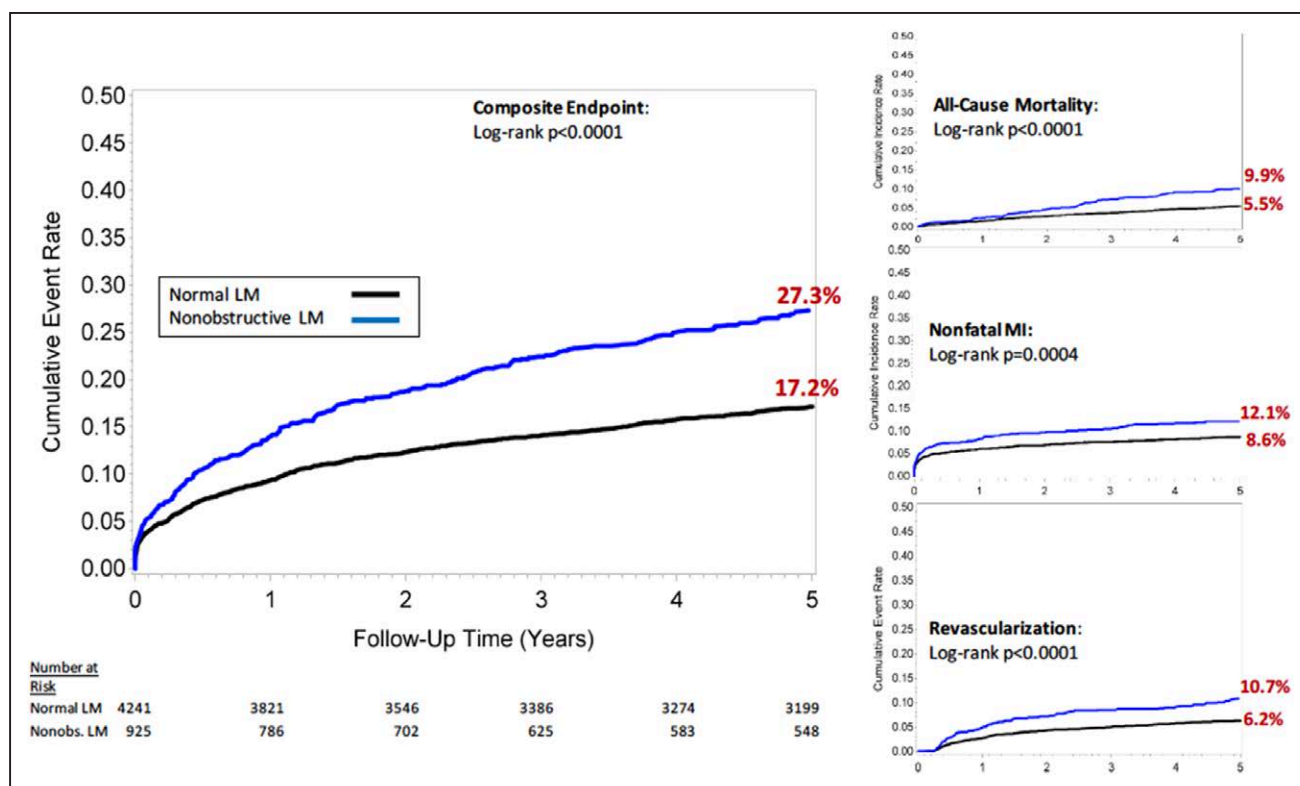
	All Patients (N=5166)	Normal LM (N=4241)	Nonobstructive LM (N=925)	<i>P</i> Value*
Age, y	60±12	60±12	65±10	<0.001
Male	3255 (63)	2592 (61)	663 (71)	<0.001
Hypertension	2769 (54)	2230 (53)	539 (59)	0.001
Diabetes mellitus	865 (17)	676 (16)	189 (21)	0.001
Hyperlipidemia	2717 (53)	2128 (50)	589 (64)	<0.001
Smoking history	1030 (20)	827 (20)	203 (22)	0.099
Family history of early CAD	1490 (29)	1204 (29)	286 (31)	0.118
LVEF, † %	60±13	60±13	61±15	0.232
Symptom characteristics				
Typical angina	696 (15)	582 (16)	114 (14)	0.424
Atypical angina	1587 (35)	1295 (35)	292 (35)	0.424
Noncardiac	409 (9)	341 (9)	68 (8)	0.424
No chest pain	1867 (41)	1515 (41)	352 (43)	0.424
Extent of obstructive CAD (per vessel)				
1-Vessel	986 (19)	723 (17)	263 (30)	<0.001
2-Vessel	496 (10)	340 (8)	156 (18)	<0.001
3-Vessel	207 (6)	205 (5)	102 (11)	<0.001
Extent of obstructive CAD (per segment)	0.8±1.5; 0 [0–1]	0.7±1.4; 0 [0–1]	1.5±1.9; 1 [0–2]	<0.001
Overall CAD burden (segment involvement score)	2.6±2.9; 2 [1–6]	1.9±2.4; 2 [0–4]	5.6±2.9; 6 [4–9]	<0.001

Values reported as mean±SD (median [interquartile range] also reported if non-normally distributed) or N (%). CAD indicates coronary artery disease; LM, left main; and LVEF, left ventricular ejection fraction.

\*Comparison of patients with normal LM and nonobstructive LM using  $\chi^2$  test for categorical variables and *t* test or Wilcoxon tests for continuous variables.

†LVEF only available in 858 (17%) of patients.





**Figure 1.** Cumulative 5-year incidence of events by left main status. Cumulative incidence of the primary composite outcome of all-cause mortality, nonfatal myocardial infarction, or coronary revascularization is displayed using a 90-day landmark time. Cumulative events rates for the secondary end points of death, nonfatal myocardial infarction, and revascularization are also shown. Patients are stratified as having normal LM or nonobstructive LM. LM indicates left main; and Nonobs, nonobstructive.

### Sex-Specific Differences in Outcomes

Next, we examined sex-specific differences in outcomes according to LM status. Women had a lower burden of obstructive CAD and segment involvement scores than men ( $P<0.001$ ; Table I in the [Data Supplement](#)). In both women and men, those with nonobstructive LM had a higher incidence of composite events than those with normal LM: women (34.3% versus 15.4%;  $P<0.0001$ ) and men (24.6% versus 18.2%;  $P<0.0001$ ; Figure 2). Importantly, a significant interaction existed between sex and LM status for the primary outcome ( $P=0.001$ ). After multivariable adjustment, the association between nonobstructive LM and the composite end point remained significant in women (adjusted hazard ratio, 1.48 [95% confidence interval 1.21–1.75];  $P=0.005$ ) but was not significant in men (adjusted hazard ratio, 0.98 [95% confidence interval 0.81–1.18];  $P=0.806$ ; Tables 2 and 3). Similarly, the association between nonobstructive LM and the individual end points of death, nonfatal MI, and revascularization also differed by sex and are presented in Tables 2 and 3. The sex-specific hazard ratios for the composite outcome by other measures of CAD extent are displayed in Table II in the [Data Supplement](#).

### Subgroup and Sensitivity Analyses

In a subgroup of 3325 patients without any obstructive CAD, the cumulative 5-year incidence of the composite outcome remained significantly higher among those with nonobstructive LM than among those with normal LM (18.6% versus 10.7%;  $P<0.0001$ ; Figure 3) and was also consistent in

sex-stratified Kaplan–Meier analysis: women (28.3% versus 10.5%;  $P<0.0001$ ); men (14.0% versus 10.8%;  $P=0.036$ ).

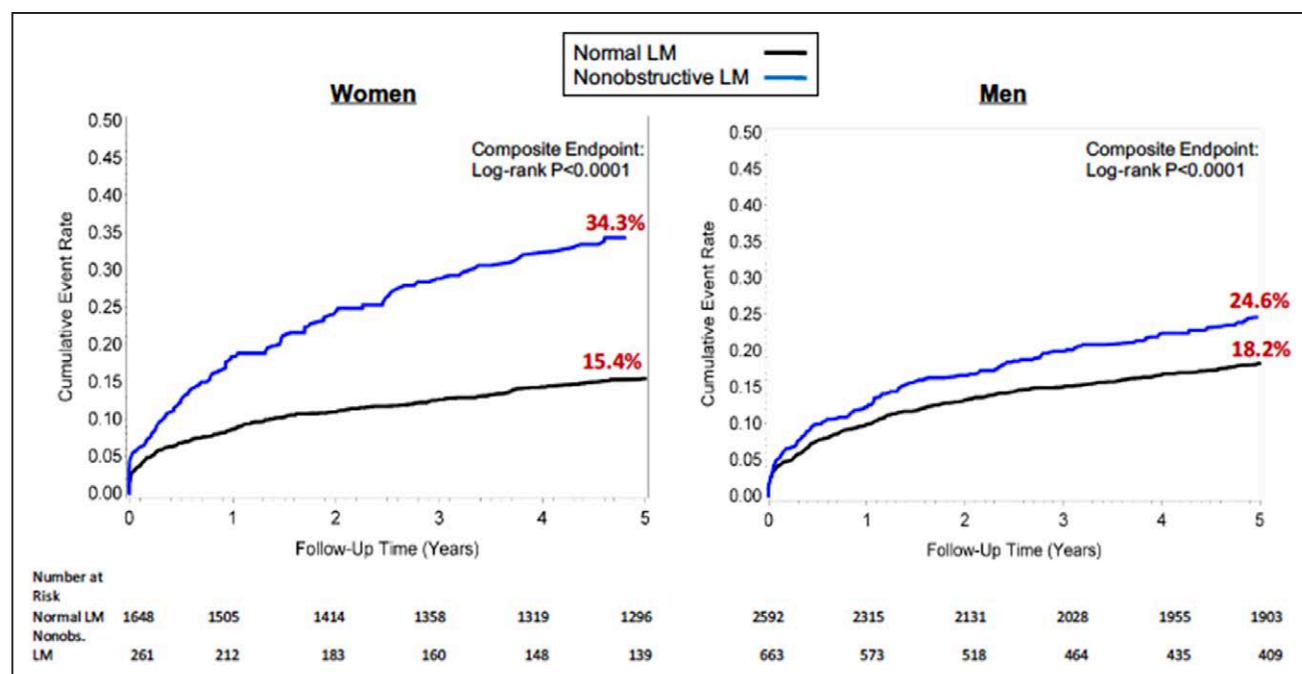
Next, we examined whether sex-related differences in outcomes varied by nonobstructive plaque pattern. As shown in Figure 4, in subgroups of patients with nonobstructive LM CAD, women had a significantly higher risk for adverse events than did men (adjusted hazard ratio, 1.78 [1.31–2.25];  $P=0.017$ ). In contrast, outcomes were not significantly different between women and men in other subgroups of nonobstructive plaque.

In addition, we examined the baseline characteristics of patients excluded ( $n=6920$ ) from our analysis (Table III in the [Data Supplement](#)). In a pooled Kaplan–Meier analysis, those with nonobstructive LM CAD had a consistent and elevated incidence of death compared with those with normal LM (13.9% versus 7.9%;  $P<0.0001$ ). Similar sex-specific differences were also observed: women (18.7% versus 8.1%;  $P<0.0001$ ), men (11.8% versus 7.7%;  $P<0.0001$ ; Figure I in the [Data Supplement](#)).

Finally, we removed revascularization events from the composite end point. Consistently, patients with nonobstructive LM had higher cumulative incidence of death or MI than patients with normal LM (19.8% versus 13.2%;  $P<0.0001$ ; Figure II in the [Data Supplement](#)) and when separated by sex: women (26.1% versus 13.1%;  $P<0.0001$ ), men (17.4% versus 13.3%;  $P=0.001$ ).

### Discussion

Although prognosis is well established in the setting of obstructive LM CAD, our findings were the first to reveal sex-specific



**Figure 2.** Cumulative 5-year incidence of events by left main status in women and men. Cumulative incidence of the composite outcome of all-cause mortality, nonfatal myocardial infarction, or coronary revascularization are displayed by LM status in women and men. LM indicates left main; and Nonobs, nonobstructive.

differences in long-term outcomes for nonobstructive LM CAD. Notably, nonobstructive LM plaque was associated with a nearly 50% higher risk for adverse events among women independent of CAD burden in other vessels, whereas the association between nonobstructive LM CAD and future events was not significant among men after risk adjustment. Furthermore, women with

nonobstructive LM plaque had an  $\approx 1.8$ -fold higher risk for future events than men with nonobstructive LM plaque; sex-specific differences in outcomes were not observed across other patterns of nonobstructive CAD. These findings provide evidence that non-obstructive LM plaque may represent an important risk marker in women that should be considered during risk stratification efforts.

**Table 2. Risk of Death, Myocardial Infarction, and Revascularization by Left Main Status in Women**

	Unadjusted		Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Composite end point										
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	2.37 (1.87–3.01)	<0.001	2.02 (1.57–2.58)	<0.001	1.63 (1.26–2.10)	<0.001	1.67 (1.30–2.15)	<0.001	1.48 (1.21–1.75)	0.005
All-cause mortality										
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	2.52 (2.31–2.90)	<0.001	1.96 (1.55–2.36)	0.001	1.87 (1.45–2.29)	0.003	1.92 (1.51–2.32)	0.002	1.58 (1.15–2.2.01)	0.036
Nonfatal MI										
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.75 (1.21–2.52)	0.003	1.60 (1.10–2.33)	0.015	1.25 (0.85–1.83)	0.254	1.29 (0.88–1.89)	0.195	1.22 (0.81–1.83)	0.334
Revascularization										
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	2.62 (2.18–3.06)	<0.001	2.33 (1.87–2.80)	<0.001	1.86 (1.38–2.34)	0.011	1.94 (1.47–2.44)	0.006	1.69 (1.19–2.19)	0.039

Model 1 covariables include age, hypertension, diabetes mellitus, hyperlipidemia, smoking, and angina; Model 2 covariables include those in model 1 plus the number of non-LM vessels with obstructive CAD; Model 3 covariables include those in model 1 plus the total number of non-LM segments with obstructive CAD; and Model 4 covariables include those in model 1 plus the segment involvement score. CI indicates confidence interval; HR, hazard ratio; LM, left main; and MI, myocardial infarction.

**Table 3. Risk of Death, Myocardial Infarction, and Revascularization by Left Main Status in Men**

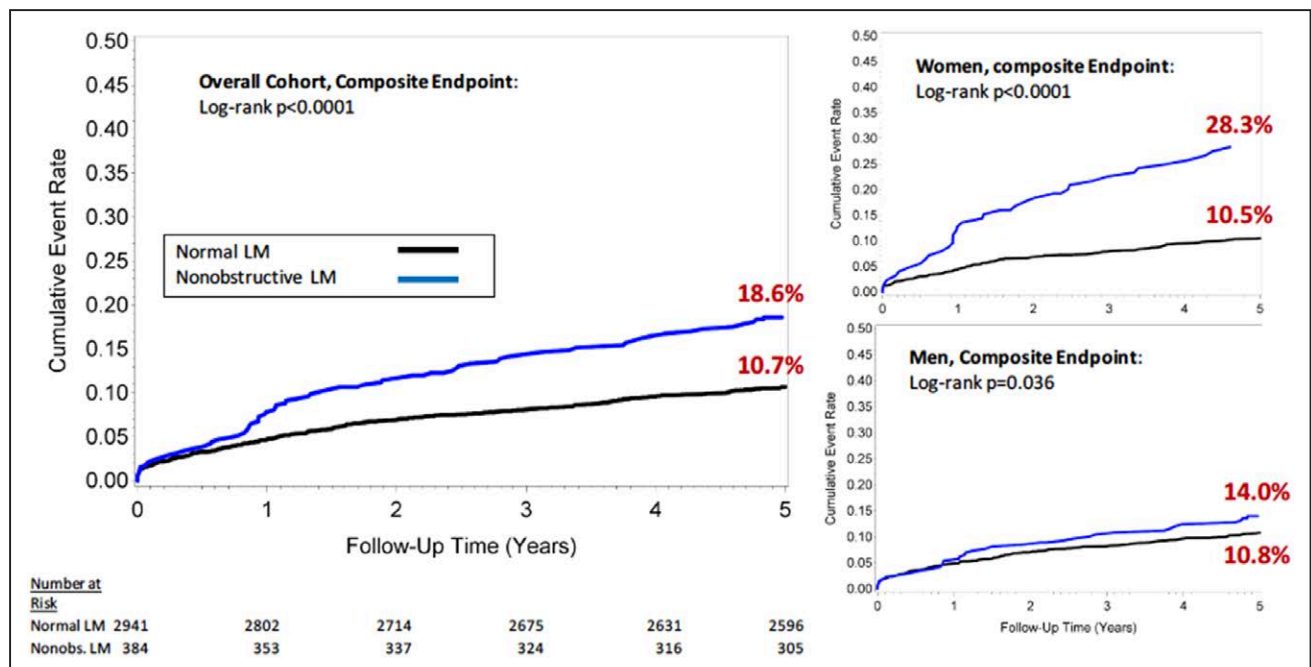
	Unadjusted		Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
<b>Composite end point</b>										
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.44 (1.21–1.71)	<0.001	1.18 (0.99–1.42)	0.065	0.99 (0.82–1.19)	0.879	1.07 (0.90–1.29)	0.438	0.98 (0.81–1.18)	0.806
<b>All-cause mortality</b>										
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.57 (1.16–2.12)	0.004	1.14 (0.84–1.55)	0.412	1.04 (0.75–1.44)	0.817	1.13 (0.83–1.54)	0.448	0.98 (0.70–1.36)	0.894
<b>Nonfatal MI</b>										
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.32 (1.01–1.72)	0.041	1.20 (0.91–1.58)	0.203	0.98 (0.74–1.30)	0.887	1.06 (0.80–1.41)	0.677	1.02 (0.76–1.37)	0.909
<b>Revascularization</b>										
Normal LM	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Nonobstructive LM	1.46 (1.11–1.91)	0.007	1.18 (0.89–1.57)	0.232	0.98 (0.73–1.31)	0.888	1.05 (0.79–1.40)	0.743	0.94 (0.69–1.27)	0.682

Model 1 covariables include age, hypertension, diabetes mellitus, hyperlipidemia, smoking, and angina; Model 2 covariables include those in model 1 plus the number of non-LM vessels with obstructive CAD; Model 3 covariables include those in model 1 plus the total number of non-LM segments with obstructive CAD; and Model 4 covariables include those in model 1 plus the segment involvement score. CI indicates confidence interval; HR, hazard ratio; LM, left main; and MI, myocardial infarction.

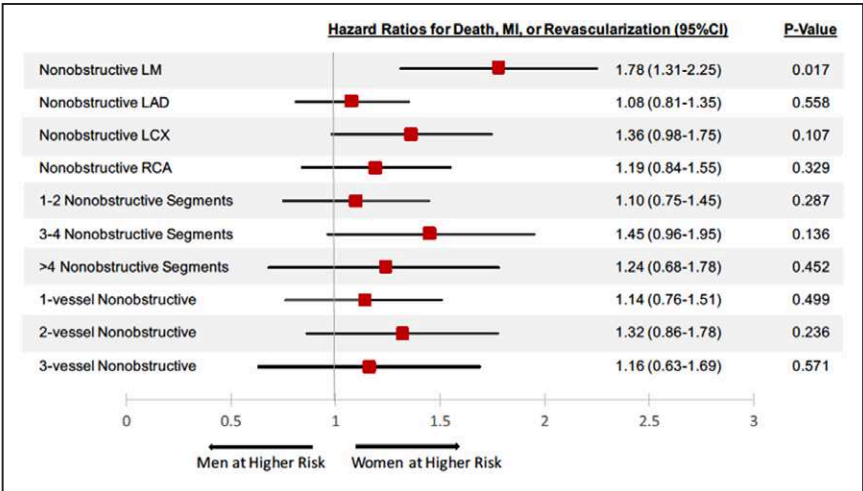
Surprisingly, there has been a paucity of data regarding the prognostic implication of nonobstructive LM plaque within the published literature. One reason may be that previous studies have frequently represented nonobstructive CAD as having a uniform level of risk. For instance, in the WISE study (Women's Ischemia Syndrome Evaluation),<sup>9</sup> 5-year event rates for MI were estimated to be 3.9% for patients with any nonobstructive

CAD. However, the extent and lesion-specific distribution of nonobstructive CAD were not further delineated.

More recently, both invasive angiographic and CCTA series have characterized gradations of risk based on the extent of nonobstructive CAD. Maddox et al<sup>12</sup> described 1-year MI event rates of 0.24%, 0.56%, and 0.59%, respectively, among patients with 1-vessel, 2-vessel, and 3-vessel nonobstructive



**Figure 3.** Cumulative 5-year incidence of events among patients without any obstructive CAD. Cumulative incident event rates for the composite outcome of all-cause mortality, nonfatal myocardial infarction, or coronary revascularization are displayed among patients without any obstructive CAD. Patients are stratified as having normal LM or nonobstructive LM. Cumulative incidence curves are also displayed in women and men, separately. CAD indicates coronary artery disease; LM, left main; and Nonobs, nonobstructive.



**Figure 4.** Sex-specific differences in risk by nonobstructive plaque location and extent. Risk-adjusted hazard ratios comparing women to men for the composite outcome of all-cause mortality, nonfatal myocardial infarction, or revascularization are shown in different subgroups of nonobstructive CAD. All models adjusted for age, hypertension, hyperlipidemia, diabetes mellitus, smoking, and angina. CAD indicates coronary artery disease; CI, confidence interval; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; MI, myocardial infarction; and RCA, right coronary artery.

CAD (defined as 20%–49% stenosis on invasive angiography). Similar proportional increases in mortality rates were reported with increasing nonobstructive vessel involvement in CCTA cohorts.<sup>20</sup> In contrast to our study, these prior investigations had shorter follow-up times, and nonobstructive LM plaque was classified as 1-vessel nonobstructive CAD, as a lesion within the left anterior descending artery territory, or incorporated within the segment involvement score.<sup>2,3,8,10,20</sup> One exception was a small, single-center CCTA study of 76 patients with nonobstructive LM CAD, of whom, none experienced an event after 20 months of follow-up.<sup>21</sup> Thus, our investigation expands on previous findings with longer, 5-year follow-up, and to our knowledge, this is the first study sufficiently powered to assess the prognostic significance of nonobstructive LM CAD.

Specifically, our study revealed that nonobstructive LM plaque was strongly associated with adverse events in women but not in men, independent of CAD burden in other vessels. These sex-specific differences in prognosis were not observed for other subgroups of patients with multisegment or multivessel nonobstructive CAD. Our results are in concordance with prior studies by Leipsic and others, who did not find that outcomes in women versus men differed based on the extent of nonobstructive CAD; however, disparities in prognosis based on the location of nonobstructive plaque (eg, LM versus other vessel) were not previously explored.<sup>11,14</sup> Shaw et al<sup>2–4</sup> described both higher in-hospital and 4-year mortality among women with significant atherosclerotic burden or high-risk lesions, such as obstructive multivessel or LM CAD as compared with men; we now extend these observations of sex-based differences in outcomes of LM disease to patients with nonobstructive plaque.

Although elucidating possible mechanisms for the association between nonobstructive LM plaque and adverse outcomes in women requires additional investigation, several potential explanations exist. Independent of body surface area, women are known to have significantly smaller coronary arterial sizes than men, including the luminal area of the LM, which has been associated with worse outcomes in women than men after coronary revascularization and may also increase susceptibility to thrombotic occlusion.<sup>22</sup> Numerous pathology examinations and intravascular ultrasound studies have also characterized differences in coronary atherosclerotic composition and progression between women and men.<sup>23,24</sup> Although women have

been noted to have less severe and extensive CAD than men, positive coronary artery remodeling was detected in the majority (73%) of women without obstructive CAD in an intravascular ultrasound substudy of WISE.<sup>24</sup> These nonobstructive but positively remodeled plaques have been proposed to serve as precursor lesions vulnerable to future erosion or rupture.<sup>25</sup> Given that the LM subtends a large proportion of the myocardium, any sex-related differences in plaque vulnerability in the LM could conceivably place women at a significant and higher risk for downstream coronary events; additional characterization of LM plaque morphology is needed to improve discrimination of at-risk lesions. Moreover, previous studies from the National Cardiovascular Data Registry have shown that patients with nonobstructive CAD are less than half as likely to receive aspirin, statins, or  $\beta$ -blockers as compared with patients with obstructive CAD.<sup>26–28</sup> The preponderance of hidden or positively remodeled plaque in women may also lead to an underestimation of true atherosclerotic burden and further therapeutic delay, potentially contributing to disparities in outcomes between women and men with nonobstructive CAD.

Our findings add to the growing body of evidence that depict a heterogeneous distribution of risk among patients with nonobstructive CAD; both the extent and location of nonobstructive plaque seem to confer varying prognostic value. Importantly, estimated rates of obstructive CAD on elective cardiac catheterization have been as low as  $\approx$ 40%, with a disproportionately lower yield for obstructive CAD among women compared with men.<sup>6,29</sup> Guideline recommendations on the management of this large cohort of patients with nonobstructive CAD have remained poorly defined; however, simple reassurance and complacency in clinical management are not likely appropriate given the prognostic implications of nonobstructive plaque. In this context, elucidating and recognizing high-risk patterns of nonobstructive CAD, such as the sex-specific significance of nonobstructive LM plaque, may not only help provide a more granular estimation of cardiovascular risk but may also identify promising targets to focus preventive care as higher risk patients may derive a greater benefit from risk-modifying therapies. Future prospective randomized trials are still needed to determine optimal strategies for therapeutic risk reduction among patients with nonobstructive CAD.



## Study Limitations

Inherently, we were unable to account for all confounders given our retrospective study design; however, we used several multivariable regression models that incorporated all available and pertinent clinical characteristics. Selection bias may have also impacted our analysis because we excluded many higher risk patients with obstructive LM or a history of CAD; however, after pooling all patients, those with nonobstructive LM remained at higher risk of death than those with normal LM, and similar sex-specific differences in outcomes were observed. Nonetheless, both external and prospective validation of our results remains to be performed, but we chose the CONFIRM registry for our initial analysis because it represents the largest CCTA cohort and with the longest duration of patient follow-up. Moreover, we did not have further details on plaque vulnerability, which may have yielded additional sex-specific predictive information and should be included in future prognostic models derived from invasive (eg, intravascular ultrasound or optical coherence tomography) or noninvasive imaging cohorts. Similarly, both left ventricular ejection fraction and myocardial ischemia carry important prognostic value and may have influenced downstream clinical outcomes; however, neither were core variables defined by CONFIRM and were, thus, not consistently documented by all enrolling sites. Finally, the CONFIRM registry did not collect information regarding medication use or post-CCTA changes in clinical management, which may have differed by sex and impacted patient outcomes.

## Conclusion

Although abundant prognostic data have documented poor clinical outcomes among patients with obstructive LM CAD, our findings were the first to reveal an elevated 5-year risk for death, MI, or revascularization associated with nonobstructive LM CAD. Specifically, nonobstructive LM plaque may represent an important risk marker in women, potentially contributing to disparities in outcomes between women and men with nonobstructive CAD. Recognizing the sex-specific prognostic significance of nonobstructive LM plaque may improve future risk stratification efforts in patients undergoing evaluation for CAD.

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## CLINICAL PERSPECTIVE

Although it is well established that obstructive left main (LM) coronary artery disease has major prognostic implications, our study reveals that nonobstructive LM plaque is also associated with adverse cardiovascular events. Importantly, the presence of nonobstructive LM coronary artery disease was associated with a nearly 50% increase in risk for future events in women, independent of coronary artery disease burden or extent in other vessels; however, the association between nonobstructive LM plaque and clinical outcomes was not significant in men. These findings show the heterogeneous profile of risk that exists for nonobstructive coronary artery disease because both plaque extent and location carry different prognostic value in women and men. Future risk stratification efforts should recognize nonobstructive LM plaque in women as an important marker of risk.

## Prognostic Significance of Nonobstructive Left Main Coronary Artery Disease in Women Versus Men: Long-Term Outcomes From the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) Registry

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## **SUPPLEMENTAL MATERIAL**



<b>Supplemental Table 1. Baseline Characteristics of Study Cohort by Gender</b>						
	All Women (N=1,911)	All Men (N=3,255)	P- Value*	Women with Nonobstructive LM (N=261)	Men with Nonobstructive LM (N=663)	P-Value**
Age, years	62±11	59±12	<0.001	67±10	63±10	<0.001
Hypertension	1,135 (60)	1,634 (50)	<0.001	185 (71)	354 (54)	<0.001
Diabetes	329 (17)	536 (16)	0.474	57 (22)	132 (20)	0.516
Hyperlipidemia	1,033 (54)	1,683 (52)	0.095	170 (65)	418 (63)	0.578
Smoking History	263 (14)	767 (24)	<0.001	53 (20)	150 (23)	0.434
Family History of Early CAD	602 (32)	887 (28)	0.001	87 (34)	198 (30)	0.288
Symptom Characteristics			<0.001			0.003
Typical angina	282 (17)	414 (14)		43 (18)	71 (12)	
Atypical angina	646 (38)	941 (33)		93 (40)	199 (34)	
Non-cardiac	188 (11)	221 (8)		21 (9)	47 (8)	
No chest pain	571 (34)	1,295 (45)		77 (33)	274 (46)	
Extent of Obstructive CAD (per-Vessel)			<0.001			0.046
1-vessel	291 (16)	695 (22)		73 (29)	190 (30)	
2-vessel	115 (6)	381 (12)		37 (15)	119 (19)	
3-vessel	74 (4)	232 (7)		21 (8)	80 (13)	
Extent of Obstructive CAD (per-Segment)	0.6±1.2; 0 [0-1]	1.0±0.9; 0 [0-1]	<0.001	1.2±1.7; 1 [0-2]	1.6±1.9; 1 [0-2]	0.008
Overall CAD Burden (Segment Involvement Score)	1.9±1.8; 2 [0-4]	2.9±2.8; 3 [1-6]	<0.001	5.3±2.9; 5 [3-8]	5.8±2.9; 7 [4-9]	0.004

Values reported as mean ± standard deviation (median [interquartile range] also reported if non-normally distributed), or N (%)

\*Comparison of women and men using

chi-squared test for categorical variables and *t*-test or Wilcoxon tests for continuous variables

\*\*Comparison of women with nonobstructive LM CAD and men with nonobstructive

LM CAD using chi-squared test for categorical variables and  $t$ -test or Wilcoxon tests  
for continuous variables

CAD: Coronary artery disease; LM: Left main; LVEF: Left ventricular ejection fraction;

Supplemental Table 2. Sex-Specific Hazard Ratios for the Composite Outcome by CAD Extent				
	Women		Men	
	Univariable HR (95% CI)	P-Value	Univariable HR (95% CI)	P-Value
No CAD	1.00	Ref	1.00	Ref
Nonobstructive CAD				
1-Vessel Nonobstructive	2.01 (1.41-2.86)	<0.001	1.82 (1.30-2.53)	<0.001
2-Vessel Nonobstructive	2.95 (1.93-4.53)	<0.001	2.56 (1.82-3.63)	<0.001
3-Vessel Nonobstructive	3.58 (2.31-5.55)	<0.001	3.02 (2.05-4.45)	<0.001
Obstructive CAD				
1-Vessel Obstructive	5.26 (3.91-7.09)	<0.001	5.04 (3.87-6.58)	<0.001
2-Vessel Obstructive	5.85 (4.00-8.56)	<0.001	5.09 (3.79-6.83)	<0.001
3-Vessel Obstructive	8.10 (5.38-12.20)	<0.001	7.13 (5.24-9.72)	<0.001
Segment Involvement Score				
1-3 Segments	2.28 (1.67-3.11)	<0.001	2.21 (1.66-2.93)	<0.001
4-9 Segments	3.78 (2.78-5.13)	<0.001	3.20 (2.42-4.22)	<0.001
>=10 Segments	4.37 (2.69-7.10)	<0.001	4.08 (2.90-5.73)	<0.001

CAD: Coronary artery disease; CI: Confidence Interval; HR: Hazard ratio

<b>Supplemental Table 3. Baseline Characteristics of Included versus Excluded Patients</b>			
	Included (n=5,166)	Excluded (n=6,920)	P- Value*
Age, years	61±12	57±14	<0.001
Male	3255 (63)	3,813 (55)	<0.001
Hypertension	2769 (54)	4,054 (59)	<0.001
Diabetes	865 (17)	1,319 (19)	0.001
Hyperlipidemia	2717 (53)	4,125 (60)	<0.001
Smoking History	1030 (20)	1,816 (26)	<0.001
Family History of Early CAD	1,490 (29)	3,101 (45)	<0.001
Symptom Characteristics			<0.001
Typical angina	696 (15)	1,375 (24)	
Atypical angina	1,587 (35)	1,642 (28)	
Non-cardiac	409 (9)	1,286 (22)	
No chest pain	1,867 (41)	1,538 (26)	
LM Stenosis Severity			<0.001
Normal LM	4,241 (82)	5,145 (83)	
Nonobstructive LM	925 (18)	628 (10)	
Obstructive LM	0 (0)	426 (7)	
Extent of Obstructive CAD (per-vessel)			<0.001
1-vessel	986 (19)	1,290 (21)	
2-vessel	496 (10)	870 (14)	
3-vessel	307 (6)	753 (12)	
Extent of Obstructive CAD (per-segment)	0.8±1.5;	1.2±1.9;	<0.001



	0 [0-1]	0 [0-2]	
Overall CAD Burden (Segment Involvement Score)	2.6±2.9; 2 [1-6]	2.6±2.6; 3 [1-6]	<0.001

Values reported as mean ± standard deviation deviation

(median [interquartile range] also reported if non-normally

distributed), or N (%)

\*Comparison of included and excluded patients using

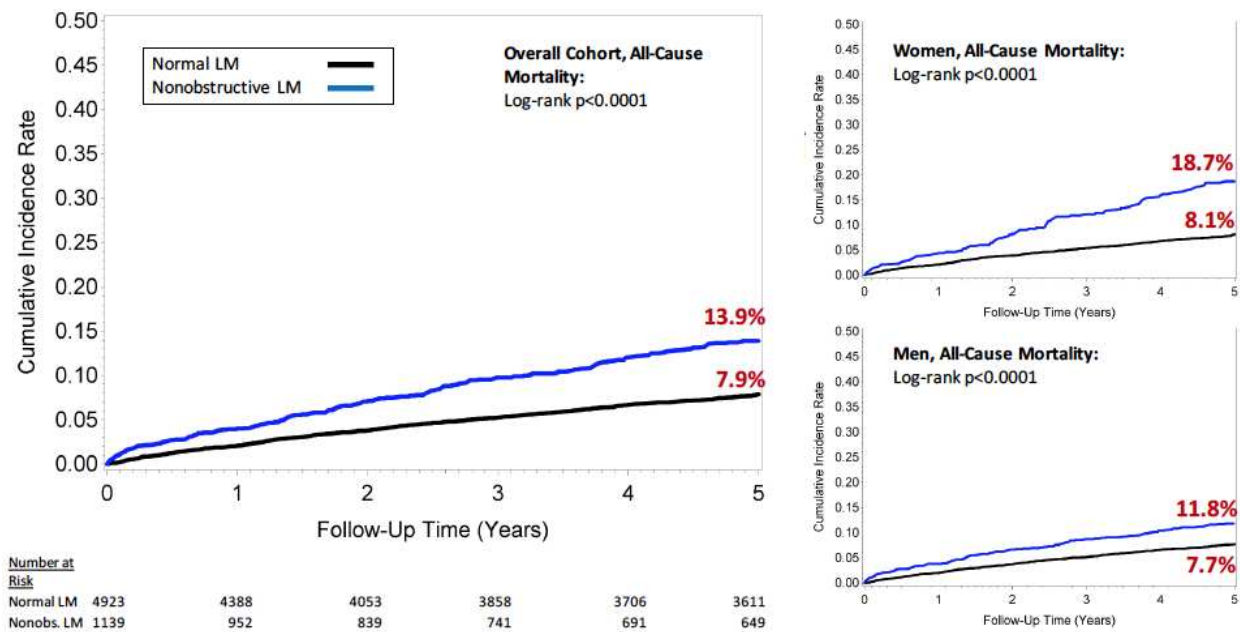
chi-squared test for categorical variables and *t*-test or Wilcoxon tests for continuous

variables

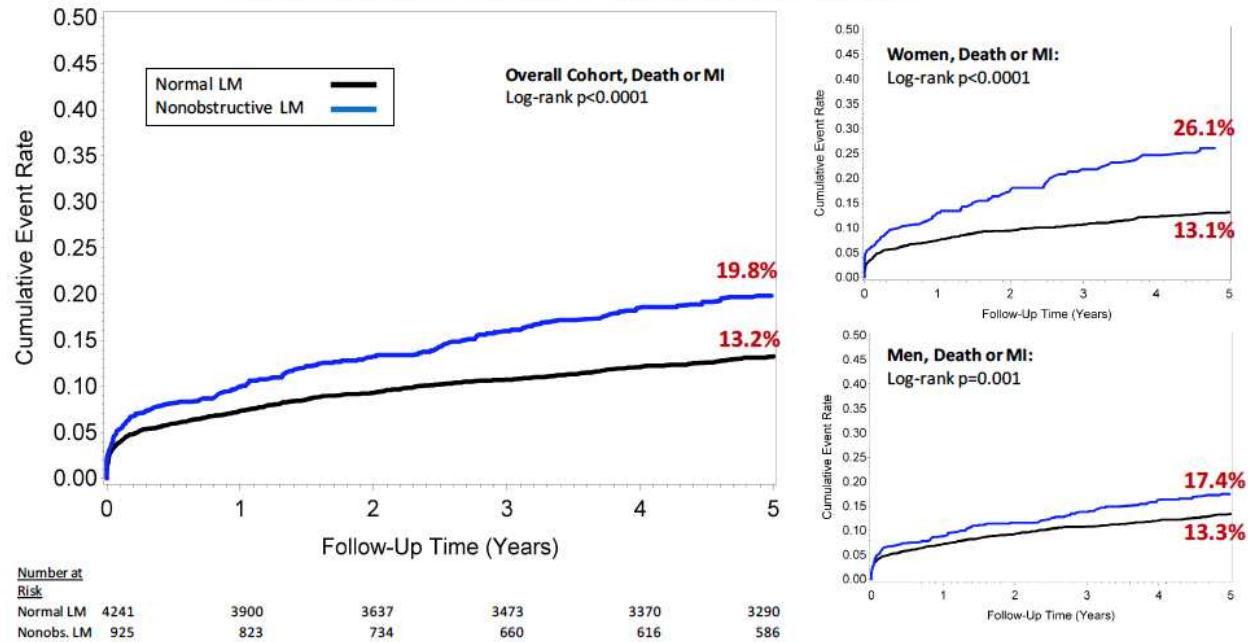
CAD: Coronary artery disease; LM: Left main; LVEF: Left ventricular ejection fraction

Supplemental Figures

Supplemental Figure 1. Cumulative 5-Year Incidence of Death Including All Patients



Supplemental Figure 2. Cumulative 5-Year Incidence of Death or MI



## **Supplemental Figure Legends**

### **Supplemental Figure 1. Cumulative 5-Year Incidence of Death Including All Patients**

Cumulative incidence of all-cause mortality in a pooled cohort that includes all previously excluded patients. Patients are stratified as having normal LM or nonobstructive LM.

Cumulative incidence curves are also displayed in women and men, separately.

CAD: Coronary artery disease; LM: Left main; Nonobs: Nonobstructive

### **Supplemental Figure 2. Cumulative 5-Year Incidence of Death or MI**

Cumulative incidence of death or MI as the composite endpoint. Patients are stratified as having normal LM or nonobstructive LM.

Cumulative incidence curves are also displayed in women and men, separately.

Cumulative incidence curves are also displayed in women and men, separately.

CAD: Coronary artery disease; LM: Left main; MI: Myocardial infarction; Nonobs: Nonobstructive



